Insulin preparations: which one to choose?

Zini, Eric

Insulin preparations: which one to choose?

Eric Zini

General aspects

Diabetes mellitus (DM) in dogs and cats is suspected in the presence of clinical signs such as polyuria, polydipsia, polyphagia, and weight loss. Other clinical signs caused by DM are visual impairment secondary to diabetic cataract (dogs), plantigrade stance and generalized weakness due to diabetic polyneuropathy (cats), systemic hypertension (dogs), vomiting and lethargy induced by diabetic ketoacidosis, and pollakiuria and stranguria for cystitis. Blood alterations, such as hyperglycemia and increased serum concentration of fructosamine, and glycosuria are used to diagnose DM. It is important to remember that hyperglycemia and glycosuria may be induced by stress in cats; in these cases, fructosamine concentrations will be normal. Other laboratory abnormalities in diabetic dogs and cats are hypertriglyceridemia, hypercholesterolemia, and increased ALT and ALP (less likely in cats). The initial assessment of diabetic dogs and cats should be as complete as possible in order to identify any complications and concomitant or predisposing diseases that need to be treated along with DM. Concurrent diseases may cause resistance to insulin treatment or worsen the prognosis.

Aims of treatment

Treatment goals are resolution of clinical signs, control of body weight, and prevention of diabetic complications and episodes of hypoglycemia. In addition, in all diabetic cats and bitches with DM associated with diestrus and pregnancy, treatment should be aimed at achieving remission of disease. Remission of DM occurs in about 50% of diabetic cats and is defined as the disappearance of clinical signs for at least 4 weeks along with normalization of blood glucose despite discontinuation of insulin therapy. Remission occurs in the first 3–6 months after first diagnosis and is more likely if cats are elderly, have no polyneuropathy, have recently been treated with corticosteroids, and if strict glycemic control is initially provided (Zini *et al.* 2010). Even cats with ketoacidosis can achieve remission. In dogs, remission is rare with the exception of bitches in diestrus or pregnancy; remission in these cases is more likely if spaying is performed within 4 weeks from onset of clinical signs or if hyperglycemia at diagnosis is not very high. The cornerstones of treatment in diabetic dogs and cats are administration of insulin and a dedicated diet (Rucinsky *et al.* 2010; Sparkes *et al.* 2015). The choice of insulin is often a dilemma for clinicians.

Insulin preparations

Short-acting insulins are preferred in animals with diabetic ketoacidosis or hyperosmolar syndrome, while insulins with an intermediate or long duration are administered in uncomplicated cases. The most widely used insulins and recommended for uncomplicated DM include:

- Porcine insulin zinc suspension. Duration of effect 8–14 hours in dogs, 6–12 in cats. First choice in dogs, with an initial dosage of 0.25 UI/kg, twice daily. Not first choice in cats, because it can have a short duration.
- Human recombinant protamine zinc insulin. Duration of effect 10–16 hours in dogs, 10–14 in cats. First choice in cats with a starting dosage of 0.25 UI/kg, twice daily, without exceeding the dosage of 2 UI/cat for each administration. Not available in some countries.
- Insulin glargine (recombinant human insulin analogue). Duration of effect 8–16 hours in cats (Gilor *et al.* 2010). First choice in this species (like the above) with an initial dosage of 0.5 UI/cat for weight <2 kg, 1 UI/cat if ≤4 kg, and 1.5 UI/cat if > 4 kg. Do not exceed 1 UI/cat if the initial glucose concentration is <350 mg/dL. In dogs it is less beneficial than other insulins. It is not currently registered for dogs or cats.
- Insulin detemir (recombinant human insulin analogue). Not first choice in both species. In cats with a starting dosage of 0.35 UI/kg, twice daily. In dogs with a starting dosage of 0.1 UI/kg, twice daily; the small amounts make it difficult to administer or prone to errors (Fracassi *et al.* 2015). It is not currently registered for dogs or cats.

Care must be taken with the use of insulins for human use because they have concentrations of 100 UI/mL, while those registered for dogs and cats have concentrations of 40 UI/mL; it is

therefore advisable to use the correct syringes for each type of insulin or make the correct conversion. Furthermore, it is suggested to administer insulin under the skin of the lateral chest and switch sides at each administration; this decreases the chances of local inflammation that in turn reduces insulin absorption.

Oral antidiabetic drugs

Oral hypoglycemic drugs are not commonly used in diabetic dogs and cats. In cats, glipizide (sulfonylurea) stimulates insulin secretion by β-cells. Glipizide is ineffective in diabetic dogs because they have almost a complete absence of β-cells. In cats, glipizide is used orally at an initial dosage of 2.5 mg/cat, twice daily; the dosage may be increased up to 5 mg/cat, twice daily, but vomiting and hepatocellular damage may occur. Glipizide is effective in approximately 30% of cats and promotes the deposition of amyloid. It may be used in cats that do not tolerate injections or when owners have poor compliance (Feldman *et al.* 1997). Acarbose, an inhibitor of the intestinal α-glucosidase, has been used in diabetic dogs and cats under insulin treatment with beneficial effects on mean glucose and fructosamine concentrations, although in the former species soft-watery were documented.

Future perspectives, insulin and pumps

The use of telemetrically-controlled pumps to deliver insulin glargine in the subcutaneous tissue of healthy cats has been recently reported (Zini *et al.* 2017). The pump during 4 weeks did not cause discomfort but life-threatening hypoglycaemia occurred soon after implantation in one cat. Stability of insulin glargine appeared to be acceptable based on in vitro experiments (Figure 1). Recently, a new pump has been developed and tested in a diabetic cat with poor metabolic control and owner compliance. Following 1-month of treatment the cat achieved remission of diabetes. A short-acting recombinant human insulin analogue able to endure for 45 days at 36 Celsius degrees was used (unpublished observation). Insulin was still effective in the cat after 30 days.

References

Feldman EC, Nelson RW, Feldman MS. Intensive 50-week evaluation of glipizide administration in 50 cats with previously untreated diabetes mellitus. J Am Vet Med Assoc 1997;210:772-777.

Fracassi F, Corradini S, Hafner M, et al. Detemir insulin for the treatment of diabetes mellitus in dogs. J Am Vet Med Assoc 2015;247:73-78.

Gilor C, Ridge TK, Attermeier KJ, et al. Pharmacodynamics of insulin detemir and insulin glargine assessed by an isoglycemic clamp method in healthy cats. J Vet Intern Med 2010;24:870-874.

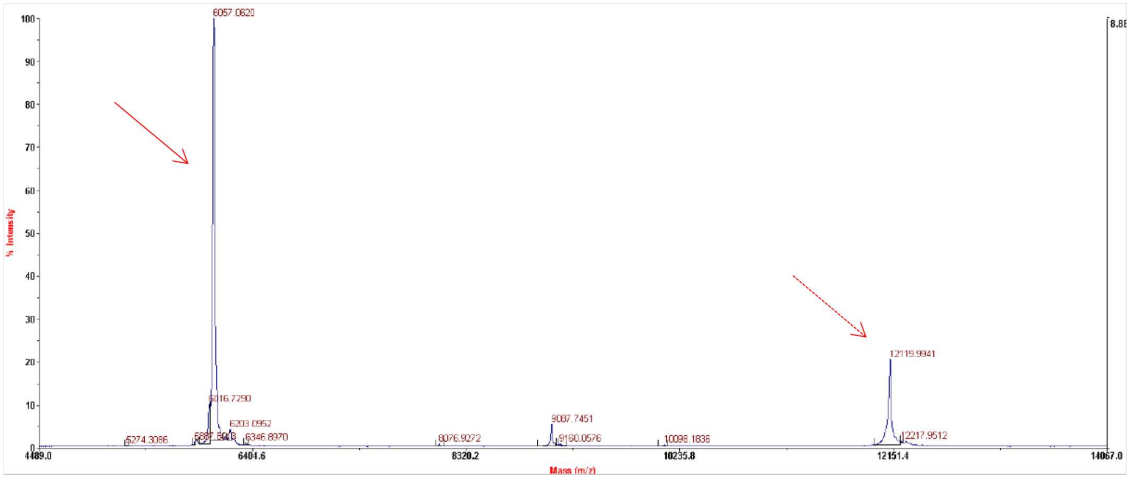
Rucinsky R, Cook A, Haley S, et al. AAHA diabetes management guidelines. J Am Anim Hosp Assoc. 2010;46:215-224.

Sparkes AH, Cannon M, Church D, et al. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. J Feline Med Surg 2015;17:235-250.

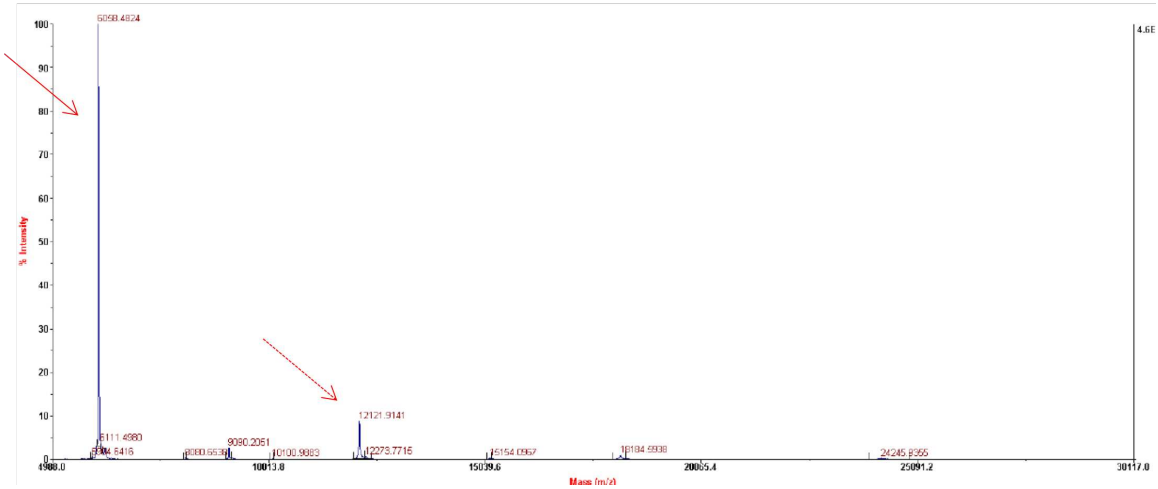
Zini E, Padrutt I, Macha K, et al. Use of an implantable pump for controlled subcutaneous insulin delivery in healthy cats. Vet J 2017;219:60-64.

Figure 1.

A



B



MALDI-TOF mass spectrometry in linear mode at the start of the trial (A) and after 8 weeks of agitation at 37°C (B) to determine the stability of insulin glargine. The peak with a molecular weight of approximately 6063 Daltons corresponds to the molecular weight of insulin glargine (red arrow). A second peak of approximately 12120 Daltons is identified at both time points, likely corresponding to aggregates of insulin glargine (dashed red arrow). Other peaks are indentified, likely corresponding to degradation products of insulin glargine.